

TENT COOPERATION TREAT

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY



(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 14 FEB 2005

WIPO

PCT

Applicant's or agent's file reference 432 WO	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/DK2004/000177	International filing date (day/month/year) 17.03.2004	Priority date (day/month/year) 21.03.2003
International Patent Classification (IPC) or national classification and IPC C07D307/88		
Applicant H. LUNDBECK AS		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 29.09.2004	Date of completion of this report 10.02.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/DK2004/000177

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-22 as originally filed

Claims, Numbers

1-58 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/DK2004/000177

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-49 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-49
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-49
Industrial applicability (IA)	Yes: Claims	1-49
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/DK2004/000177

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s e separate sheet

1) Reference is made to the following documents:

- D1: EP-A-1 118 614
D2: WO 01/32642 A
D3: WO 00/39112 A
D4: WO 98/19513 A
D5: ANZALONE ET AL.: 'Substituent Effects on Hydrogenation of Aromatic Rings: Hydrogenation vs. Hydrogenolysis in Cyclic Analogues of Benzyl Ethers' J. ORG. CHEM., vol. 50, 1985, pages 2128-2133, XP002282189 cited in the application
D6: SUGIMORI, AKIRA ET AL: 'Radiation-induced reduction of aromatic carboxylic esters in alcoholic solutions' CHEMISTRY LETTERS (1980), (5), 483-6, XP001189503 cited in the application
D7: LEROY S FORNEY: 'Reaction of Terephthalic Acid with Formaldehyde in Sulfur Trioxide Media' JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 35, no. 5, May 1970 (1970-05), pages 1695-1696, XP002936415 ISSN: 0022-3263 cited in the application

2) Non-unity (Rule 13 PCT) (Reference to section IV)

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-49

Claim 1 and dependent upon relate to a method for preparing an alkoxycarbonylphtalide of formula (III), comprising reacting a compound of formula (VIIIa) with a formaldehyde and oleum and then adding an alcohol of formula R^3OH .

2. Claims: 50-56

Claim 50 and dependent upon disclose a method for preparing an intermediate suitable for the synthesis of citalopram or escitalopram, comprising the steps of preparing a compound of formula (III) and then isolating it.

3. Claims: 57-58

Claims 57 and 58 relate to compounds of formula (III).

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/DK2004/000177

D3 describes on page 5, lines 25-35, the preparation of 5-ethoxy-carbonylphthalid, a compound which falls into the definition of present formula (III).

Compounds of present formula (III) are also known from the following cited documents:

D4 on page 7, examples 1 and 2;

D5 on page 2129, example 22;

D6 on page 484, example 6;

D7 on page 1696, left-hand column, last paragraph, second line from the bottom where the synthesis of 5-carbomethoxyphthalide is mentioned.

The concept linking independent claims 1, 50 and 57 seems to be represented by compounds of formula (III), which are however known in the state of the art as mentioned above.

Hence, in the absence of a single general inventive concept linking said claims, involving the same or equivalent special technical features and resulting in a teaching over the prior art, the Examiner considers that three separate inventions are to be seen in the present application, namely:

Invention **(A)**: the process as described in claim 1 and dependent upon;

Invention **(B)**: the process as described in claim 50 and dependent upon;

Invention **(C)**: compounds of formula (III).

Since compounds of formula (III) are known, the three concepts have no inventive feature in common and therefore the claims on file comprise three inventions, which must be considered non-unitary (Rule 13 PCT).

INVENTION (A)

3) Novelty (Reference to section V)

D1 and D2 relate to a process for the preparation of a 5-carboxyphthalide of formula (A) (cf. claim 1 of D1 and D2), and not to an ester thereof as it is in present claim 1.

Example 1 on page 5 of D3 discloses the preparation of 5-ethoxycarbonylphthalid from 5-carboxyphthalid and ethanol. On page 4 of D3, lines 24-27 it is mentioned that the 5-carboxyphthalide used as a starting material can be prepared by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO_3 , a process which is not however carried out in D3.

Thus, only formally present claim 1 seems new over D3.

The same considerations apply to D4, describing on page 7 (cf. examples 1 and 2) the synthesis of 5-tert-butoxycarbonylphthalid and 5-(2-propyloxycarbonyl)phthalid from 5-carboxyphthalid and respectively tert-butanol and 2-propanol.

In the examples of D4 the 5-carboxyphthalid is not prepared.

D5 discloses the preparation of 5-carbethoxyphthalide (compound 22 on page 2129) by a different process than that of present claim 1.

D6 relates to the synthesis of 5-methyloxycarbonylphthalid (compound 6 on page 484) by radiation-induced reduction of aromatic carboxylic esters, which does not fall into the scope of present claim 1.

D7 differs from present claim 1 in that the 5-carbomethoxyphthalide (cf. on page 1696, left-hand column, last 3 lines) is prepared by reaction with methanol- BF_3 .

Accordingly, the subject-matter of present claims 1-49 meets the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

Each of the documents D3 and D4 may be considered to represent the closest state of the art. As mentioned in paragraph 3 above, the teaching of present claim 1 differs from that of D3 and D4 in that first a compound of formula (VIIIa) is reacted with formaldehyde and

oleum and then an alcohol of formula R^3-OH is added to the reaction.

Thus, the problem to be solved by the present application may be seen in the provision of an improved process for the preparation of compounds of formula (III).

From D1 and D2 it is already known that a 5-carboxyphthalide can be prepared by reaction of terephthalic acid with oleum and formaldehyde.

D3 further proceeds with the esterification of 5-carboxyphthalide (mentioning on page 4, lines 24-27 that the 5-carboxyphthalide used as a starting material can be prepared by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO_3) in ethanol.

Moreover, D4 reports the reaction of 5-carboxyphthalide with tert-butanol and 2-propanol and D7 the esterification with methanol- BF_3 .

In view of the prior art disclosure the subject-matter of present claim 1 appears thus to be obvious and the dependent claims as well do not contain any features which, in combination with the features of claim 1, to which they refer, meet the requirements of the PCT in respect of inventive step.

No unexpected effects of the process presently claimed over the state of the art are given in the application.

Accordingly, present claims 1-49 do not meet the criteria of Article 33(3) PCT.

5) Further observations (Reference to section VIII)

5.1) Claims 24-26 and 41 do not appear to be supported by the description as required by Article 6 PCT.

5.2) Independent claim 1 is not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

In the present case it seems that the characterising part is represented by the addition of the alcohol R^3-OH .

5.3) It is at present not clear which claims example 8 of the description refers to.

5.4) It is also not clear why the Applicant mentions a step (c) in claim 56, which is absent in previous claims 52-55, which claim 56 refers to.